SUMMARY

ZENECA INC

FINISHED PRODUCT: **ACCOLATE** ™

ACTIVE INGREDIENT(S): **ZAFIRLUKAST (ICI 204,219)**

Trial title (Trial number): A Randomized, Double-Blind, Parallel-Group Trial to Compare the Safety and Effectiveness of Zafirlukast (ACCOLATE™) with that of Pseudoephedrine and Placebo in Subjects with Seasonal Allergic Rhinitis: A Day in the Park Trial (9188IL/0120)

Clinical phase: III **Time period:** 25 July 1995 through 27 August 1995

Principal investigator, location and center number: PPD , PPD PPD , PPD , Minneapolis, MN 55402 (Center PPD)

OBJECTIVES: (a) to compare the effect of oral zafirlukast, pseudoephedrine, and placebo upon daily signs and symptoms of acute seasonal allergic rhinitis, as assessed by diary cards; (b) to determine the time of onset of action of oral zafirlukast during periods of peak pollen exposure; (c) to determine the safety and tolerability of oral zafirlukast as compared to pseudoephedrine and placebo.

METHODS:

Design: Two-day, single-center, randomized, double-blind, double-dummy, placebo-controlled parallel trial comparing zafirlukast, pseudoephedrine, and placebo.

Population: One hundred and seventy-four men or women aged 12 to 64.

Key inclusion criteria: Demonstrated symptoms of allergic rhinitis or conjunctivitis as manifested by two symptoms graded 2 (mild to moderate) or one symptom graded 3 (moderate to severe) during a 3-hour qualification period.

Key exclusion criteria: (a) chronic sinusitis requiring antibiotic therapy; (b) treatment with corticosteroids, astemizole, cromolyn, nedocromil sodium, theophylline, hepatitis B surface antigen, or antihistamines other than chlorpheniramine or pseudoephedrine within the specified time periods; (c) clinically significant laboratory or electrocardiogram (ECG) abnormalities or significant history of other illness.

Dosage: Three weeks before Trial Day 1, all patients switched from their usual regimen of allergy medications to short-acting antihistamines or decongestants. On Trial Days 1 and 2 patients were supplied with the following drugs according to one of the four groups to which they were randomized (zafirlukast 20 mg BID, zafirlukast 80 mg BID, pseudoephedrine 60 mg TID, or placebo): 20-mg zafirlukast tablets (CCI , Lot number CCI , Batch CCI), matching placebo tablets (CCI , Lot number CCI , Batch CCI), 30-mg pseudoephedrine tablets (CCI , Lot number CCI , Batch CCI), or pseudoephedrine-matching placebo tablets (CCI , Lot number CCI , Batch CCI (BID for the zafirlukast group, TID for the pseudoephedrine group).

Key assessments:

Efficacy: After adminstration of trial medication, allergic symptoms were collected by having patients complete symptom-score diary cards on an hourly basis while at the park and continuing documentation at home at 1830, 2030, and 2230. Additionally, patients completed a global efficacy assessment at the end of the trial.

Safety: Safety was assessed by subjective symptomatology and adverse events monitoring. Results of clinical laboratory tests, vital signs measurements, electrocardiography (ECGs), and physical examinations were evaluated at screening.

Statistical considerations: The symptoms-score diary-card data were analyzed in the framework of an analysis of covariance (ANCOVA) model for a randomized, parallel group design. Pairwise comparisons among all dose groups were performed within the ANCOVA framework. Also, a contrast testing linear trend with dose among the zafirlukast and placebo treatment groups was performed.

Survival analysis methodology was used to assess differences among treatments with respect to the time of onset of action.

Chi-square tests of independence and logistic regression were used to assess pairwise treatment group differences and linear trend with dose, respectively, for patients' global evaluations of efficacy.

RESULTS:

Demography: A total of 174 patients (91 women [52%] and 83 men [48%], with a mean age of 30 years [range PPD through PPD years]) with allergic rhinitis were enrolled in the trial; 171 patients (98%) completed both days of treatment.

Efficacy results: No statistically significant differences occurred on either day of the trial between any active treatment group and placebo in runny nose scores or itchy/watery eyes scores.

Both doses of zafirlukast showed differences from placebo in sneezing scores that were statistically significant or approached statistical significance for several time points on the

evening of Trial Day 1 and in the park on Trial Day 2. The magnitude of the treatment effect tended to increase with increasing doses of zafirlukast.

The only other statistically significant difference between zafirlukast and placebo was for stuffy nose scores at only one time point, 1230 on Trial Day 1, when zafirlukast 20-mg showed greater improvement than placebo. No statistically significant differences occurred between either zafirlukast treatment group and placebo, nor were any statistically significant dose response relationships detected, for itchy nose/throat/palate scores, total symptoms scores, or total nasal symptoms.

The pseudoephedrine 60-mg treatment group showed statistically significant improvement over the placebo group in stuffy nose scores, sneezing scores, itchy nose/throat/palate scores, total symptoms scores, and total nasal symptoms scores for numerous time points during the trial. The pseudoephedrine 60-mg treatment group also showed sporadic statisically significant improvement over zafirlukast in stuffy nose scores and itchy nose/throat/palate scores.

Survival analysis on time to onset of efficacy showed no statistically significant differences among the four treatment groups, and the global evaluation of effectiveness was not statistically significant for any treatment comparisons.

Safety results: (a) No deaths or serious adverse events occurred during this trial. Placebo-treated Patient PPD PPD 5 days after trial end, resulting in death and considered by the investigator as unrelated to trial treatment. (b) Fifteen placebo-treated patients had 19 adverse events, 9 zafirlukast 20-mg-treated patients had 12 adverse events, 11 zafirlukast 80-mg-treated patients had 13 adverse events, and 12 pseudoephedrine-treated patients had 16 adverse events. All of the events were considered mild to moderate in intensity with the exception of Patient PPD mentioned above and Patient PPD (zafirlukast 80-mg group) who had severe pruritus on Trial Day 2, also considered by the investigator to be unrelated to trial treatment. (c) Headache was the most common adverse event, reported by 24 patients: 9 (20.5%) placebo-treated, 5 (11.6%) zafirlukast 20-mg treated, 6 (14.0%) zafirlukast 80-mg treated, and 4 (9.1%) pseudoephedrine-treated. (d) At baseline, 9 patients had laboratory values outside of the normal range that were considered clinically significant by the investigator. None of these elevations were considered by the investigator as sufficiently significant to inhibit trial entrance. (e) All screening electrocardiogram results were normal and no abnormal findings were recorded as a result of physical examination and vital signs measurement.

CONCLUSIONS:

Zafirlukast showed improvement over placebo in the relief of sneezing due to allergic rhinitis. This relief presented itself on the evening of Trial Day 1 and continued through Trial Day 2. The magnitude of the treatment effect tended to increase with increasing doses of zafirlukast. Zafirlukast did not show consistent improvement versus placebo for any other allergic rhinitis symptoms measured in this trial.

Pseudoephedrine 60 mg showed improvements versus placebo that were statistically significant or approached statistical significance for several nasal symptoms: stuffy nose (evening of Trial Day 1, in-the-park and evening on Trial Day 2), sneezing (evening of Trial Day 1), itchy nose/throat/palate (in-the-park and evening on Trial Day 1, in-the park on Trial Day 2).

Neither of the active treatments was effective at relieving non-nasal symptoms of allergic rhinitis. No significant treatment differences were found with respect to the global evaluation of effectiveness or the time to onset of action.

All active treatments were well tolerated and not clinically different from placebo with respect to their safety profiles.